rare and the tendency for spinal cord involvement much less prominent.[3,4]

CT scanning is quite sensitive for subarachnoid bleeding in the intracranial space. Patients with aneurysmal subarachnoid bleeding generally have hemorrhage detected in the basal cisterns.[5,6] The atypical location of subarachnoid blood on CT scans, in the setting of a Southeast Asian with typical diffuse CNS signs and evidence of inflammation with eosinophilia in the cerebral spinal fluid, should raise the question of *Angiostrongylus* or *Gnathostoma* infestation; the presence of myelitis favors the latter.

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The Value of Artificial Beta Cell in the Management of Insulinoma

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INSULINOMA, a tumor of the pancreatic beta cell causing hypoglycemia, presents a number of diagnostic and therapeutic problems. When use of exogenous insulin can be excluded, a combination of hypoglycemia and inappropriately high serum insulin levels (above 6 to 10 μU per ml) is diagnostic.[1] However, a number of insulinoma patients have fasting euglycemia.

Insulinomas are usually small and difficult to see by radiographic techniques. Even inspection and palpation of the pancreas during surgical procedure may fail to locate the tumor. Occult and multiple lesions are often difficult to find at operation and may require major pancreatic resection, sometimes without relief of symptoms.[2]

This case demonstrates the difficulties of clinical and laboratory diagnosis in a patient with insulinoma, the diagnostic value of subselective angiography and the use of the artificial beta cell in the management of patients.

Report of a Case

The patient is a 26-year-old woman whose principal complaint was periodic loss of consciousness. The first episode occurred at the age of 12 and was preceded by symptoms of catecholamine excess. Later on, episodes of loss of consciousness occurred about every other month and were then introduced by a prodromal period of depersonalization, drowsiness and sometimes generalized jerking movements. The patient said she had no feeling of increased hunger, restlessness, blurred vision, palpitations or any gastrointestinal symptoms. Repeated brain scans and electroencephalograms showed no abnormalities. Nevertheless, a diagnosis of a seizure disorder was made and the patient was started on a regimen of diphenylhydantoin (phenytoin; Dilantin) and phenobarbital, which she had been taking since. There was no relief of the symptoms, and the dosages of phenobarbital and Dilantin were increased progressively. Over the years the frequency of the

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episodes of unconsciousness increased to three to five times a month and their duration up to 24 to 27 hours. There was no relationship of the episodes of unconsciousness to time of day, meals or exercise. Several months before admission, the patient was found to have low fasting serum glucose levels. A prolonged fast was followed by plasma insulin and glucose determinations, with findings consistent with the diagnosis of insulinoma. Subsequently, the patient had an arteriographic examination that included injections of the celiac, splenic and superior mesenteric arteries and was negative both prospectively and retrospectively.

Physical examination on admission showed a well-developed woman whose height was 162 cm (64 in), weight 65 kg (143 lb) and blood pressure 100/60 mm of mercury. She was well oriented and alert, but showed some loss of recent memory. Otherwise her physical examination, including neurologic findings, was completely normal. Biochemical and radiologic studies confirmed a diagnosis of insulinoma as described in the "Results" section.

Methods

Prolonged Fast

Fasting was continued after an overnight 12-hour fast and serum glucose, immunoreactive insulin, C-peptide and cortisol levels were measured every hour.

Glucose Tolerance Test (GTT)

After an overnight fast serum glucose, insulin, C-peptide, cortisol, growth hormone and plasma glucagon levels were measured before and after oral administration of 100 grams of glucose. Blood specimens were obtained at 30 minutes and every hour after the meal for a total of six hours.

Glucagon Test

After an overnight fast 1 mg of glucagon was given as an intravenous bolus. Serum glucose and insulin levels were measured before glucagon administration and 5, 10, 20, 30, 60, 90 and 120 minutes after.

Tolbutamide Test

After an overnight fast the patient received 1 gram of sodium tolbutamide diluted in 10 ml of saline and given intravenously over two minutes. Serum glucose, insulin, C-peptide and cortisol levels were measured before the injection and 5, 10, 20, 30, 45, 60, 90, 120, 150 and 180 minutes after the injection.

Hormone Assays

All hormone measurements were done by specific radioimmunoassays (RIA) using double antibody precipitation.[3] Blood specimens for glucagon were collected in ethylenediaminetetraacetate (EDTA) tubes chilled on ice, the plasma was separated immediately in a refrigerated centrifuge, transferred into tubes containing trasylol and frozen.

The serum immunoreactive insulin was measured directly in the insulin immunoassay. An aliquot of serum was then gel filtered (Biogel P-30) to separate the proinsulin and insulin components and each column fraction was assayed in the insulin radioimmunoassay. The early eluting peak, representing the proinsulinlike component, was read off both the human proinsulin standard curve and the human insulin standard curve. The second peak, representing the insulin component, was measured against the insulin standard. The sum of the individual fractions in each peak is the proinsulin and insulin concentration, respectively. The relationship between proinsulin and insulin is expressed as percentage proinsulin, where both peptides have been calculated from the insulin standard.[4]

Pancreatic Angiography

Subselective pancreatic angiography with a highly concentrated bolus injection of contrast media (10 ml per second) and rapid sequence magnification radiography were used to detect the tumor by looking for a pancreatic parenchymal capillary blush and persistent staining. This technique was previously shown to be successful in the detection of pancreatic endocrine tumors.[5,6]

The Use of the Artificial Beta Cell

A glucose-controlled insulin infusion system (GCIIS) (Biostator®, produced by Miles Laboratories, Elkhart, Ind), was used to monitor and regulate the patient's blood glucose during the surgical procedure. Details of its operation have been described elsewhere.[7] In brief the GCIIS is a glucose sensor linked via a computer to an infusion system that allows either insulin, dextrose or both to be given as needed to maintain blood glucose level within a preselected range. A minute-by-minute record is printed of the mean whole blood glucose level, the dextrose and insulin infusion rates for the subsequent minute and the cumulative insulin dose. In the present studies, the basal dextrose level control constant (BD) was set at 80 mg per dl and the rate of dextrose solution infusion (RD) at 40 mg a minute. Thus, the instrument delivered 40 mg a minute of dextrose if the preceding minute's mean blood glucose level was determined to be 80 mg per dl. Serum glucose sensitivity constant (QD) was set at 20, allowing a relatively sensitive response to a change in glucose level away from 80 mg per dl. The double lumen catheter withdrawal system functioned well without interruption.

Morphologic Studies

Perioperative histologic examination was done by a routine technique on frozen sections of the tissue specimen. As for definitive morphologic studies, the tumor tissue specimen was prepared in three different ways. A portion was fixed immediately on tumor extirpation in 10 percent neutral buffered formaldehyde and prepared for paraffin sections, which were stained with hematoxylin and eosin and indirect aldehyde fuchsin. A second portion was cut into 1 by 1 mm blocks, fixed immediately in 0.1 mol per liter of sodium cacodylate-buffered 2 percent glutaraldehyde for eight hours, rinsed in the cacodylate buffer, postfixed in 1.5 percent osmium tetroxide and embedded in epon resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined by electron microscopy. A third portion of the tumor specimen was freshly frozen and sections of 10 to 15 μm were prepared in a cryostat and stained for immunoreactive insulin by indirect fluorescence. This was done by incubating the slices with an antiinsulin antibody prepared in guinea pigs. After a rinse the tissue slices were exposed to fluorescein-conjugated rabbit anti-guinea pig IgG antibody.

TABLE 1.—*Laboratory Results During Prolonged Fast*

Period of Fasting (hours)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*	*Serum Cortisol (μg/dl)*
12	59	12.5	2.4	18.4
13	55	7.5	2.5	22.4
15	58	6.4	2.3	15.6
16	38	6.6	2.8	13.4
17	28	7.9	2.5	22.0
18	27	6.8	2.6	15.6

The test was performed twice with comparable results. Serum immunoreactive (IR) insulin and C-peptide levels are inappropriately high for the degree of hypoglycemia. There is no increase in serum cortisol in response to hypoglycemia.

Results

Prolonged Fast

After a total of 18 hours of fasting, the patient's speech became slurred, she became drowsy and suddenly lost consciousness. The coma promptly subsided with an infusion of 50 percent glucose solution. The patient did not show any clinical signs of catecholamine excess. Serum glucose level at the time of the coma was 27 mg per dl while immunoreactive insulin level was 6.8 μU per ml. There was no increase in serum cortisol level and the level of serum C-peptide did not change significantly (Table 1).

Glucose Tolerance Test

The patient had slight glucose intolerance with postprandial hyperglycemia persisting at two hours of the test (Table 2). Her serum glucose level later progressively fell to 53 mg per dl. The usual rebound of serum glucose level toward pretreatment value did not occur. The rise in immunoreactive insulin and C-peptide levels was within low normal range. Changes in the serum cortisol level were paradoxical, being elevated during the hyperglycemic phase and suppressed during the

TABLE 2.—*Glucose Tolerance Test Results*

Time (hours)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*	*Serum Cortisol (μg/dl)*	*Plasma Glucagon (pg/ml)*	*Serum Growth Hormone (ng/ml)*
0	65	11	1.9	28.8	24	<0.75
½	125	21	2.9	34.4	<20	<0.75
1	182	27	3.1	31.2	<20	<0.75
2	190	49	3.2	20.8	<20	2.2
3	89	11	1.3	14.4	<20	1.4
4	62	14	2.0	18.8	<20	1.8
5	53	7	2.4	13.6	<20	3.7
6	52	10	0.9	10.4	<20	3.0

Glucose (100 grams by mouth) was given after the 0-hr blood specimen was drawn. The test shows glucose intolerance, serum glucose being elevated to 190 mg/dl at 2 hrs of the test. The response of the immunoreactive (IR) insulin and C-peptide levels is within the low normal range. Insulin response is incompletely suppressed by postprandial hypoglycemia. The response of cortisol is paradoxical. Plasma glucagon level does not rise during hypoglycemia and the response of growth hormone is blunted.

late postprandial phase. Except for the fasting determination, the plasma glucagon level was unmeasurable. The expected response of glucagon is suppression during the hyperglycemic phase and elevation during the postprandial hypoglycemic phase. Serum growth hormone level rose during the late postprandial phase, which is normal, but the response was blunted. Slight glucose intolerance persisted even shortly after surgical removal of the insulinoma.

Glucagon Test

The insulin response to an intravenous injection of 1 mg of glucagon was a rise only to low normal (Table 3). Serum glucose level rose to that seen in normal persons.

Tolbutamide Test

Following infusion of sodium tolbutamide, the serum insulin level promptly rose and then slowly fell to a value of 11 μU per ml at 150 and 180 minutes. A parallel change in the serum C-peptide level was observed (Table 4). Serum glucose value progressively fell and remained in the hypoglycemic range. The test was repeated after successful resection of the tumor. At that time, temporary decline in serum glucose level was followed by a rebound to pretreatment values and the decline of serum insulin and C-peptide levels after a temporary rise was faster and more significant, as seen in normal situations (Table 4).

TABLE 3.—*Glucagon Test Results*

Time (minutes)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*
0	81	7.5
5	98	9.4
10	95	12.0
20	144	14.0
30	149	12.0
60	86	7.1
90	72	5.6
120	53	6.1

One milligram of glucagon was injected intravenously after the first blood specimen was drawn. Serum glucose level rose after glucagon injection due to mobilization of hepatic glucagon and stimulation of gluconeogenesis. However, insulin response was blunted and serum glucose value became subnormal during late phase of the test. IR = immunoreactive.

Serum Proinsulin

The fasting values were as follows: serum glucose 68 mg per dl and direct serum immunoreactive insulin 25.7 μU per ml; proinsulin on the insulin standard was 6.7 μU per ml and insulin on the insulin standard was 17.0 μU per ml. The percentage contributed by proinsulin was 6.7:23.7 or 28.4 percent. When proinsulin was calculated from the proinsulin standard, its value was 1.2 ng (31.3 μU per ml). Postprandially, the respective values were 196 mg per dl (glucose), 61.2 μU per ml (direct insulin), 16.4 μU per ml (proinsulin) and 46.3 μU per ml (insulin). The percentage contributed by the proinsulin was 16.4: 62.7 or 26.2 percent. Thus, both fasting and postprandial concentrations of proinsulin were elevated. Our normal values are between 5 percent and 22 percent.

Angiographic Studies

Because previous routine abdominal arteriography studies using injection of the celiac and superior mesenteric arteries were negative, the

TABLE 4.—*Results of the Tolbutamide Test Before and After Resection of Insulinoma*

	Before Resection			*Two Weeks After Resection*		
Time (minutes)	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*	*Serum Glucose (mg/dl)*	*Serum IR Insulin (μU/ml)*	*Serum C-Peptide (ng/ml)*
0	48	9.7	4.6	82	4.5	1.8
5	44	27.0	5.2	83	37.0	4.5
10	47	21.0	5.7	..	....	...
15	..	..	..	92	8.4	2.3
20	35	20.0	5.6	..	....	...
30	32	13.0	4.9	49	9.9	3.7
45	39	15.0	4.4	..	....	...
60	39	13.0	3.9	65	7.3	2.5
90	39	14.0	4.0	75	6.9	2.3
120	37	13.0	3.3	77	5.1	1.8
150	39	11.0	2.8	78	6.4	1.8
180	36	11.0	3.8	..	....	...

One gram of tolbutamide was injected intravenously after the first blood specimen was drawn. The normal response of serum immunoreactive (IR) insulin to tolbutamide is an increase to more than 35 μU per ml. The response in this patient before resection was blunted. During the late phase of the test, serum insulin levels were inappropriately high for the degree of hypoglycemia and there was no rebound of serum glucose to normal. After resection of the tumor, the serum insulin response to tolbutamide became normal and there was also a normal rebound of serum glucose to euglycemic level.

patient underwent subselective pancreatic angiography. A highly concentrated bolus injection of contrast material into the dorsal pancreatic artery permitted the complete arterial system of the pancreas to be seen, with reflux into the splenic and hepatic arteries, producing a capillary blush appearance to the pancreatic parenchyma and gross acinar architecture. Two persistent stains were seen (Figure 1). One of these (small arrow) was located in the proximal pancreatic tail and the second was located close to the hilum of the spleen. Either of them could represent an insulinoma. The differential diagnostic consideration for the second lesion was an accessory spleen.

Surgical Intervention

Adjacent to the hilum of the spleen was a firm, encapsulated and somewhat irregularly shaped mass about 1.5 cm in diameter. This mass was of the same size and location as the tumor blush seen on the angiogram close to the hilum of the spleen. The lesion was excised. Inspection and palpation of the rest of the pancreas, including the site of the blush in the body of the pancreas, did not reveal any abnormality.

Use of Artificial Beta Cell During Surgical Procedure

The GCIIS was connected to the patient through the basilic vein an hour before the operation began. At that time, the patient's serum glucose level was 42 mg per dl. Dextrose in water was infused rapidly via the GCIIS to bring the serum glucose level up to 80 mg per dl and the infusion was continued to maintain serum glucose stable at that predetermined value. To achieve this goal, between 40 and 100 mg a minute of dextrose solution had to be infused continuously. Within half an hour after removal of the insulinoma, the need for the infused dextrose solution to maintain serum glucose levels at 80 mg per dl progressively decreased until no dextrose was necessary and even slight hyperglycemia developed in the patient (Figure 2).

Morphologic Studies

The tumor removed from the tip of the pancreatic tail was identified as an insulinoma on both perioperative and definitive histologic examinations. With light microscopy it was seen to be composed of uniform cells arranged in glandular formations. Electron microscopy showed poorly granulated cells as seen in Figure 3. Only occasional granules possessed crystalline structures typical of pancreatic beta cells and corresponding to their secretory product containing insulin (see insert, Figure 3). Immunofluorescent staining for

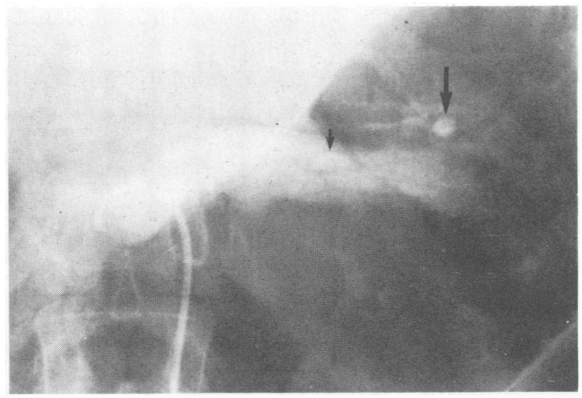

Figure 1.—Late capillary blush phase of the subselective pancreatic arteriography outlining the parenchymal anatomy of the body and tail of the pancreas. Two superimposed well-circumscribed blushes are seen: one in the proximal tail **(small arrow)** and one in the splenic hilum **(large arrow).** They were interpreted as possible insulinoma and either insulinoma or aberrant spleen, respectively.

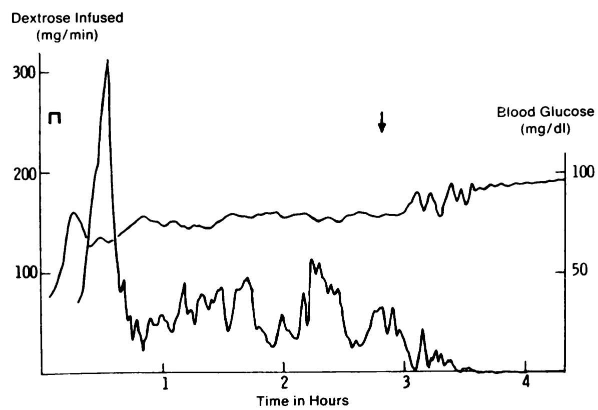

Figure 2.—Use of Biostator during surgical procedure. The upper curve represents blood glucose level as recorded automatically every minute by the Biostator. The lower curve represents the amount of intravenous dextrose infusion in milligrams per minute necessary to maintain blood glucose at a preset value of about 80 mg per dl. The "clamp" corresponds to an intravenous infusion of 5 grams of glucose via Biostator to correct the patient's fasting hypoglycemia. The arrow indicates time at which the insulinoma was removed. Note fluctuations in the dextrose required to maintain euglycemia, possibly reflecting episodic secretion of insulin from the tumor. Removal of the insulinoma was followed about five minutes later by a decreased requirement for dextrose infusion and by upswings and downswings of blood glucose level, which finally settled at about 95 mg per dl, at that time in the absence of any dextrose infusion. These patterns are considered to be typical of successful resection of the tumor.

insulin was strongly positive in the normal pancreatic islet cells. The tumor tissue showed only a slight, diffuse stain (Figure 4).

Discussion

This case report shows the difficulties of diagnosing and treating insulinoma. The misleading diagnosis of a seizure disorder in our patient and the failure to make a correct diagnosis during 14 years of her morbidity may be partially explained by the fact that insulinoma is rare, especially in young people,[1,2] whereas epilepsy is a relatively frequent disorder of childhood. Furthermore, the symptoms of our patient were not clearly related to fasting and exercise. Spontaneous recoveries from coma probably contributed to the confusion.

The cardinal symptom of the disease in our patient was depression of her sensorium, progressing into a coma. Serum glucose levels at the time the patient became unresponsive were as low as between 16 and 27 mg per dl. In the presence of such low glucose concentrations, immunoreactive insulin (IRI) levels in the plasma ranged between 6.8 and 12.5 μU per ml. This was clearly inappropriate for the degree of hypoglycemia and was by itself diagnostic of insulinoma. However, similar values of IRI were also present while the patient was euglycemic (Table 3), so it is difficult to accept that relative hyperinsulinemia alone was responsible for her hypoglycemia. In healthy people in our series, plasma insulin levels in the fasting state are up to 10 to 15 μU per ml in the presence of euglycemia. Because in our patient a higher proportion of the insulin than normal was composed of relatively biologically inert proinsulin, the amount of biologically active insulin in her serum was even lower than measured by the radioimmunoassay.

It is possible that the lack of counterregulatory mechanisms was an important factor in the genesis of hypoglycemia in our patient, in addition to the inappropriate insulin secretion. This was suggested

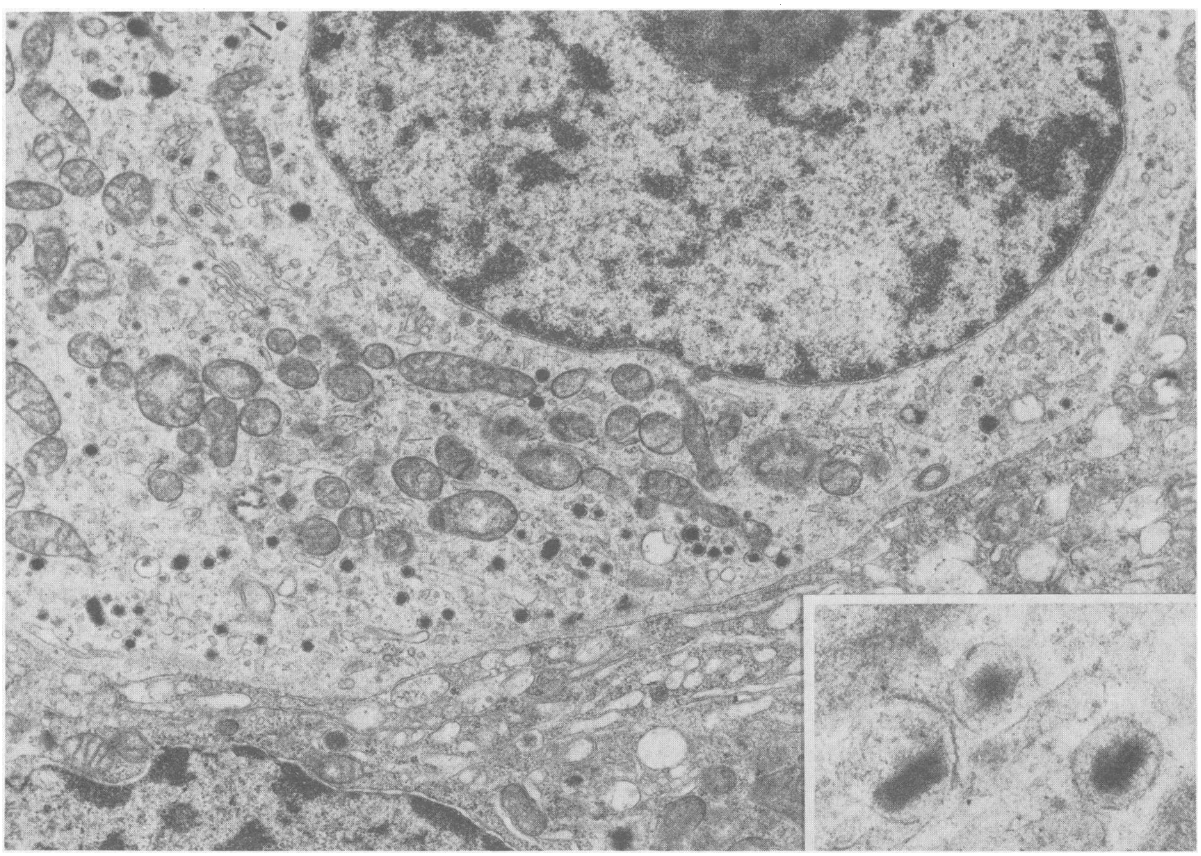

Figure 3.—Electron microscopy of the insulinoma cells (reduced from magnification ×15,680). Parts of two adjacent tumor cells are seen. The cells are rich in mitochondria, smooth endoplasmic reticulum and free ribosomes. Secretory granules can be seen containing mostly amorphous electron-dense contents. Only occasional dense granules contain crystalline structures believed to correspond to insulin (**insert,** reduced from magnification ×89,600). The secretory granules were often associated with well-developed Golgi complexes.

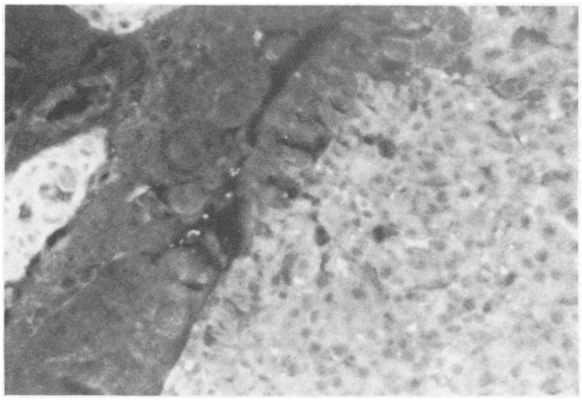

Figure 4.—Indirect immunofluorescence study of the pancreatic tissue using guinea pig antiinsulin antibody and fluorescein-conjugated rabbit antiguinea pig IgG antibody (reduced from magnification ×250). Exocrine pancreas **(dark zone)** does not react. Insulinoma, on the right, has a relatively weak reaction for insulin. Parts of two normal islets can be seen with a strong positive reaction for insulin **(white areas)**.

by the following findings: During the hypoglycemic phase of the glucose tolerance test, plasma glucagon determination failed to show increase as expected. Increase in serum cortisol level in response to hypoglycemia was blunted or absent on several occasions: during the prolonged fast, GTT or tolbutamide provocative test. The response of growth hormone to hypoglycemia during GTT was blunted. Although plasma catecholamine levels were not measured, the absence of symptoms of catecholamine excess during episodes of severe hypoglycemia suggested that their secretion was also inadequate.

It is not clear why the response to hypoglycemia of the hormones opposing the excessive anabolic action of insulin should have been inadequate. The counterregulatory hormone secretion may have escaped from dependence on hypoglycemia, as this became a chronic condition. It can also be speculated that the insulinoma produced compound(s) inhibiting the secretion of the counterregulatory hormones. Such substances can be, for example, somatostatin, which is a normal secretory product of the islet cell tissue. An attempt was made to measure plasma somatostatin levels by RIA* in this patient but was unsuccessful due to high nonspecific binding.

Another possibility is that the insulinoma produced insulin that was biologically active but relatively inactive immunologically. Release of other hypoglycemic factors such as nonsuppressible insulinlike activity (NSILA) should also be considered. It is unlikely that the patient would have shown increased sensitivity to insulin. In insulinoma patients, decreased sensitivity to insulin was reported, probably due to decreased self-regulation of insulin receptors in states of chronic hyperinsulinemia.[8]

In normal persons, the serum insulin-glucose ratio decreases during prolonged fast, which is also found in hyperinsulinemic states such as obesity. In contrast, under similar conditions the serum insulin-glucose ratio increases in insulinoma patients.[9] In our patient, some progressive decrease of serum insulin and C-peptide levels also occurred with prolonged fast and the development of hypoglycemia, but the insulin was never lower than 6 μU per ml.

Various ratios between serum glucose and IRI were recommended to be used in diagnosis of insulinoma, such as glucose:IRI, less than 2.5; IRI: glucose, greater than 0.3; 100×IRI divided by (glucose−30), greater than 50. Diagnostic failures were found to occur with all of these ratios.[1] Taking into account values obtained in our patient during prolonged fast, that is, 27 mg per dl for serum glucose and 6.8 μU per ml for serum insulin, the second and third ratios would be diagnostic of insulinoma, but not the first one. The major difficulty in establishing various ratios is the fact that between different laboratories the normal range and sensitivity of the assay for serum glucose is much more standardized than that for serum IRI. Therefore, it is again emphasized that in the presence of significant hypoglycemia, the serum insulin should be undetectable and measurable serum IRI should raise a suspicion of the presence of insulinoma when use of exogenous insulin can be excluded.

Serum insulin and C-peptide responses to provocative stimuli in our patient were within the low normal range. This was true for the oral glucose tolerance test, the glucagon test and the initial phase of the tolbutamide test. The provocative tests did not add anything more convincing to this observation and they should not be used routinely in the diagnosis of insulinoma.

Insulinoma cases have been reported wherein the reaction of insulin to provocative stimuli and to suppression was either normal or absent.[10,11] Glucose intolerance that develops in some of these patients is believed to be a result of atrophy of the normal tissue due to the chronic hyperinsulinemic state. However, atrophy of normal islets is

*Courtesy of Roger H. Unger, MD, Department of Medicine, University of Texas Southwestern Medical School at Dallas and the Dallas Veterans Administration Medical Center.

probably less frequent than suspected. The insulin content in the uninvolved tissue was found to be normal.[12] In our patient, the islets in the tissue beyond insulinoma had a normal histologic appearance and stained strongly for insulin by immunofluorescence. Why, then, the mild glucose intolerance developed in the patient is not clear, but it again raises the possibility of secretion by the tumor of a humoral inhibitor of insulin release from the normal tissue or a decreased peripheral sensitivity to the insulin action. This seems to be supported by the fact that after the surgical procedure the response of IRI to intravenous tolbutamide became normal, whereas before the surgical procedure it was blunted (Table 4).

It is impossible to determine to what extent the insulin response is influenced by normal pancreatic tissue. In some patients at least, insulinoma may release insulin independently of the regulatory mechanisms and any changes in plasma insulin could be due to superimposed secretion of insulin from normal islets.

Determination of serum proinsulin was helpful in the diagnosis of our case. The proportion of proinsulin was elevated in both fasting and stimulated states, as previously demonstrated by others.[13-16] At the electron-microscopic level, the insulinoma cells contained only a few secretory granules with crystalline structure that are believed to correspond to insulin. Most of the granules contained amorphous material, consistent with proinsulin.[17]

Locating and surgically resecting an insulinoma is a prerequisite for the cure of the disease. This can be a difficult task. In a large series of 154 cases of Laroche and co-workers,[2] curative resection of insulinoma was accomplished in only 78 percent. The course of 22 patients in whom no tumor was identified was unfavorable. Perioperative location of the tumor by palpation is frequently unsuccessful in the case of small tumors, and this is critical for successful resection.

In our patient, two techniques proved to be especially helpful to the surgeon in identifying the insulinoma: the preoperative use of subselective pancreatic angiography and the use of artificial beta cell during surgical procedure. Pancreatic angiography directed the surgeon to areas showing a persistent tumor stain, one of which proved to be the insulinoma. It has been shown by one of us (H.E.) previously that this technique can routinely locate tumors under 1 cm in diameter[5] when employing a specific technique that combines high-bolus subselective pancreatic artery injection with high-resolution magnification filming technique. No side effects were observed in more than 100 patients studied. Clinical signs of pancreatitis did not develop in any of the patients and, following the procedure, serum amylase levels remained unchanged. Preoperative location of insulinoma by angiographic techniques has been reported to be successful in between 40 percent to 90+ percent of patients.[18-20] To increase the accuracy of such a procedure, it should be subselective and use subtraction, magnification and stereotactic techniques. Transcutaneous and transhepatic pancreatic venous sampling can locate an insulinoma even more specifically by showing a stepwise gradient of immunoreactive insulin in veins draining the tumor.[18] However, successful selective venous catheterization and specimen sampling remains a difficult procedure accompanied by considerable morbidity.

In our case, the artificial beta cell proved to be extremely helpful during surgical procedure by keeping the patient's serum glucose at a preset euglycemic level through continuous intravenous infusion of a dextrose solution and by indicating the time of successful removal of the insulinoma. Between 5 and 15 minutes after resection of the insulinoma, the requirement for dextrose for maintaining euglycemia gradually decreased until none was required and the serum glucose level became stable at between 95 and 100 mg per dl. In our case, where two lesions were suspected to be present from the angiographic study, it was important to identify the resected tissue as the only critical tumor responsible for hypoglycemia and this made it unnecessary to take a biopsy or resect the area of the second tumor blush. Artificial beta cell has been used previously for the same indications.[21,22] Similar results were obtained showing a rise of serum glucose level shortly after removal of the insulinoma. In cases where no tumor can be identified preoperatively or during surgical operation, sequential resection of the pancreatic tissue in a patient continuously monitored by an artificial beta cell should indicate removal of the tumor.

Summary

We present the case of a 26-year-old woman with a 14-year history of periodic comatose states treated originally as a seizure disorder. A diagnosis of insulinoma was made, mainly on the basis of inappropriately high plasma insulin concentra-

tion (above 6 μU per ml) in the presence of significant hypoglycemia, and elevated proinsulin levels. Routine abdominal angiography studies were negative. Subselective pancreatic angiography showed two areas of persistent tissue stain. One of those proved to be an insulinoma. Surgical treatment was done while the patient was continuously monitored by an artificial beta cell. This was found to be very useful for maintaining the patient's serum glucose level in the euglycemic range and for confirming removal of the insulinoma. To maintain euglycemia, a dextrose solution had to be infused continuously via the artificial beta cell. However, between 5 and 15 minutes after removal of the insulinoma, the need for dextrose infusion gradually decreased to zero and the patient's serum glucose level settled down at 95 to 100 mg per dl. This was regarded as proof of resection of the critical tissue, and thus the second persistent stain observed on subselective angiography was defined as a false-positive finding.

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